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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/609,218 | 06/27/2003 | Vincent Ling | GNN-010CPDV | 7566 |
| 959 | 7590 | 06/28/2005 | EXAMINER | |
| LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109 | | | OUSPENSKI, ILIA I | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1644 | |

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/609,218

Applicant(s)

LING ET AL.

Examiner

ILIA OUSPENSKI

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 13-27 is/are pending in the application.
- 4a) Of the above claim(s) 4, 8 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-7, 13-18 and 20-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment, filed 05/02/2005, is acknowledged.

Claims 9 – 12 have been cancelled.

Claims 1, 3 – 5, 7 – 8, and 13 – 14 have been amended.

Claims 16 – 27 have been added.

Claims 1 – 8 and 13 – 27 are pending.

Claims 4 and 8 have been withdrawn from consideration by the Examiner as being drawn to nonelected inventions.

The newly submitted claim 19 is drawn to a nonelected species of the invention. Therefore, claim 19 is withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 1 – 3, 5 – 7, 13 – 18, and 20 – 27, as they read on the elected species of VCAM-1, are under consideration in the instant application.

It is noted that prior art search has been extended to include the species of IL-10, TNF α , and IFN- γ .

2. This Office Action will be in response to applicant's arguments, filed 05/02/2005.

The rejections of record can be found in the previous Office Action, mailed 11/02/2004.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

It is noted that New Grounds of Rejection are set forth herein.

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3. Sequence compliance: The instant application, as amended 05/02/2005, appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Domestic priority: Applicant argues that the instant application is entitled to the priority date of the priority application USSN 09/362,812. In particular, Applicant argues that the '812 application teaches that inhibition of costimulation of T cells can inhibit spontaneous abortion in a subject, which, combined with the level of skill in the art, should support and enable the claimed methods.

This is not found persuasive, because the teachings of the '812 application are limited to costimulatory molecules, such as B7-1, B7-2, and ICOS. Neither the '812 application nor state of the art provide a nexus between these molecules and the instantly claimed adhesion molecules and inflammatory cytokines. Further, the general teachings regarding costimulation do not provide adequate support under 35USC 112, first paragraph, to the specific molecules recited in the instant claims. In addition, the teachings methods to inhibit spontaneous abortion does not enable one of skill in the art to practice the claimed diagnostic and prognostic methods.

Therefore, the instant claims have been accorded the priority date of 07/28/2000, the filing date of USSN 09/628,129, as indicated in the prior Office Action.

5. Applicant's amendment to the Title has obviated the objection of record.

6. The dates have been added to references B10 – B12 and C4 – C5 on IDS filed 07/19/2004.

7. The specification stands objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP 608.01(o). Correction of the following is required:

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A. Claims 1 and 5 include a recitation of "spontaneous abortion," whereas specification appears to provide antecedent basis only for a more narrow recitation of "immune-mediated spontaneous abortion," e.g. on page 5, first paragraph.

Applicant's argument has been fully considered, but has not been found convincing. Applicant argues that the phrase "the term 'immune mediated abortion' includes spontaneous termination of pregnancy" provides support for the claimed limitations. This is not found persuasive, because the genus of "spontaneous abortion" is broader than "immune-mediated abortion."

Applicant is requested to identify the written support for claims 1 and 5, particularly the claimed limitations of "spontaneous abortion". Alternatively, Applicant is invited to amend the specification to provide antecedent basis for the claimed subject matter.

B. The remaining objections of record have been obviated by Applicant's amendments.

8. Applicant's amendments have obviated the objections of record to claims 1, 4, and 8.

9. Claim rejection under **35 USC 112, second paragraph**:

The rejections of record have been withdrawn in view of applicant's amendments and arguments.

The following New Grounds of rejection are necessitated by Applicant's amendment.

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10. Claims 1, 5, 16 – 18, and 20 – 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, and 16 – 18, and 20 – 27 are indefinite in the recitation of “abnormal” presence or level of mRNA. The term “abnormal” is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. Claim rejection under 35 USC 112, first paragraph:

The rejections of record set forth in paragraphs A, B, C (in part), and E of the prior Office Action have been withdrawn in view of Applicant’s amendments and arguments.

The rejections of record set forth in paragraphs C (in part) and D of the prior Office Action are maintained for the reasons of record.

12. Claims 1 – 3, 5 – 7, and 13 – 18 and 20 – 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

C. The disclosure does not provide a sufficient enabling description for a broadly defined genus of “adhesion molecules.”

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Applicant argues that it is not necessary to enable all species of the claimed invention, but rather a representative number of species.

Applicant's argument has been fully considered, but has not been found convincing as it applies to the genus of "adhesion molecules."

The genus of adhesion molecules is extremely large, and of the few members that have been tested, two (ICAM and PECAM) are not affected (Figs. 6B and 6C), and one (P-selectin) is elevated only marginally (Fig. 6D). Therefore, while the disclosure may be enabling for certain specific adhesion molecules, it does not provide a sufficient enabling description for the genus as broadly recited in the instant claims.

The rejection of record is maintained for the reasons of record.

D. The disclosure does not provide a sufficient enabling description for a broadly defined genus of "biological samples."

Applicant argues that given the high level of skill in the art, further experimentation to determine whether a correlation exists between the expression level of a molecule in a particular biological sample and the risk of spontaneous abortion would not be undue.

This is not found persuasive, because, given the extremely large number of possible types of "biological samples" and indicator molecules encompassed by the instant claims, and the fact that the levels in some tissues are known not to correlate with risk of spontaneous abortion (Daniel et al., of record, Am. J. Reprod. Immunol., 2000, V. 43, pp. 92 – 97), the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue. Therefore, while the disclosure may be enabling for certain specific types of biological samples, it does not provide a sufficient enabling description for the genus as broadly recited in the instant claims.

The rejection of record is maintained for the reasons of record.

13. The following New Grounds of rejection are necessitated by Applicant's amendment.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection.*

Applicant's amendment asserts that no New Matter has been added and points to the specification at page 42, lines 6 – 15 for support for the newly added limitation "mRNA level is decreased by 50% or greater." However, the specification does not appear to provide an adequate written description of this limitation.

The specification discloses on page 42, lines 6 – 15, a number of specific ranges of increased levels of indicator molecules, which are not seen as providing adequate support for the limitation "mRNA level is decreased by 50% or greater."

The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action. Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

14. Claim rejection under **35 USC 102(b)**:

The rejection of record is maintained for the reasons of record as it applies to $\text{TNF}\alpha$ and $\text{IFN-}\gamma$, as well as to the generic recitation of "inflammatory cytokines."

15. Claims 3, 7, 14 – 18 and 20 – 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaouat et al. (J. Immunol., 1995, vol. 154, pp. 4261-4268; of record, reference A16 on IDS filed 07/19/2004; see entire document).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Chaouat et al. fail to teach or suggest that altered mRNA levels of any one of cytokine can be used to diagnose or prognose spontaneous abortion.

This is not found persuasive, because Chaouat et al. teach that placentae of mice at increased risk of spontaneous abortion produce increased levels of inflammatory cytokines $\text{TNF}\alpha$ and $\text{IFN-}\gamma$ (e.g. first paragraph of Results on page 4263, and Figure 1), and that elevated mRNA levels of these inflammatory cytokines correlate with fetal death (page 4263 paragraph 1 of Results, and page 4266 left column bottom paragraph). Therefore, inherent in these teachings is the diagnostic and prognostic value of mRNA levels of at least the inflammatory cytokines $\text{TNF}\alpha$ and $\text{IFN-}\gamma$ for predicting spontaneous abortion.

The rejection of record is maintained for the reasons of record, as it applies to the amended and newly added claims.

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16. Claim rejection under **35 USC 103(a)**:

The rejection of record is maintained for the reasons of record as it applies to $\text{TNF}\alpha$ and $\text{IFN-}\gamma$, as well as to the generic recitation of "inflammatory cytokines."

17. Claims 3, 7, 14 – 18 and 20 – 27 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Chaouat et al. (1995; of record) in view of Busfield (US Pat. No. 6,194,151; see entire document).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Chaouat et al. fail to teach or suggest that mRNA levels of any cytokine can be used to diagnose or prognose spontaneous abortion. Applicant further argues that while Bushfield teaches that both protein and mRNA levels can in principle be used in diagnostic and prognostic assays, mRNA levels for a particular gene do not always directly correlate with the corresponding protein level.

This is not found persuasive, because as discussed above, Chaouat et al. do teach that the diagnostic and prognostic levels of at least $\text{TNF}\alpha$ and $\text{IFN-}\gamma$ for predicting spontaneous abortion, and provide direction to specifically to elevated mRNA levels of these inflammatory cytokines as correlative with fetal death. This provides both motivation and expectation of success when combined with the teachings of Bushfield regarding the utility of mRNA levels as diagnostic and prognostic tests in inflammatory conditions.

The rejection of record is maintained for the reasons of record, as it applies to the amended and newly added claims.

18. Conclusion: no claim is allowed.

Claims 1, 5, and 13 appear to be free of prior art.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI

Patent Examiner

Art Unit 1644

June 22, 2005

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PRIMARY EXAMINER
TECH CONTROL 1600
6/22/05